Pharmacokinetics and pharmacodynamics of nifedipine infusion in normal volunteers

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1 Two studies of the pharmacokinetics and pharmacodynamics of intravenous nifedipine infusion were performed: the first, a randomised double-blind crossover study of nifedipine and its vehicle in eight subjects, the second a dose ranging study in nine subjects.

2 Nifedipine pharmacokinetics did not vary with dose or duration of infusion up to 8 h, and are similar to those reported for other nifedipine preparations.

3 Nifedipine increased heart rate and forearm blood flow and decreased blood pressure after bolus injection but not during prolonged infusion.

4 The vehicle decreased blood pressure and increased forearm blood flow after bolus injection but not during prolonged infusion. It did not affect heart rate.

5 The vehicle's haemodynamic activity has not been previously recognised and is of potential importance in the study of this and similar preparations of calcium antagonists.

Keywords nifedipine vehicle pharmacokinetics pharmacodynamics intravenous infusion

Introduction

The dihydropyridine calcium antagonist nifedipine is used to treat vasospastic and exercise induced angina, and hypertension (Stone *et al.*, 1980). Due to the poor sensitivity and specificity of the early assays which did not distinguish the parent compound from its major metabolite (Foster *et al.*, 1983), there have been few studies of nifedipine pharmacokinetics until recently. However, newer high performance liquid chromatography (Kleinbloesem *et al.*, 1984a) or gas chromatography assays (Rosseel & Bogaert, 1983) have allowed the study of the pharmacokinetics of nifedipine administered by oral, intravenous bolus and rectal routes (Foster *et al.*, 1983; Kleinbloesem *et al.*, 1984b,c; Raemisch & Sommer, 1983). To date, only one study of the pharmacokinetics and pharmacodynamics of prolonged intravenous infusion of nifedipine has been reported (Raemisch & Ziegler, 1985). Intravenous bolus might rapidly achieve effective concentrations which could be maintained by infusion, avoiding the wide fluctuations in plasma

nifedipine concentrations seen after oral dosing (Raemisch & Sommer, 1983). Newer dihydropyridine calcium antagonists have also been studied using this route (Serruys *et al.*, 1985; Campbell *et al.*, 1985). For reasons of solubility, these drugs are often administered in a vehicle of 15% ethanol, 15% polyethylene glycol and 70% water. This vehicle may theoretically have pharmacodynamic effects of its own, but to date there have been no human studies of the vehicle alone compared with nifedipine.

In this study, we have examined the pharmacokinetics and pharmacodynamics of nifedipine given by intravenous infusion at various doses, and compared them with the effects of the vehicle alone.

Methods

Two studies were performed. The first, study A, was designed to compare the effects of intra-

venous administration of nifedipine to those of the vehicle, in a double-blind, randomised, cross over study. The second, study B, was designed to examine the effects of varying doses of nifedipine.

Subjects

Study A Eight healthy drug free volunteers (three female) participated (mean age 29 years, range 22–39, mean weight 73 kg, range 59–85). Three smoked 1–3 cigarettes per day, and six drank 1–5 pints of beer per week. Medical history, physical examination and haematological and biochemical indices were normal. The subjects were fasted overnight and until the end of the infusion.

Study B Nine other drug free healthy volunteers (four female) participated (mean age 22 years, range 21–23, mean weight 66 kg, range 62–69). Medical history, physical examination, ECG and haematological and biochemical indices were all normal. Six consumed 1–6 pints of beer per week, and two smoked 5–15 cigarettes per day. The subjects were fasted overnight and for the first 3 h of the infusion.

All subjects gave informed consent and the studies were approved by the local ethics committee.

Protocol

Study A Nifedipine (10 mg% in the vehicle of 15% ethanol, 15% polyethylene glycol and 70% water) or the vehicle alone were administered in a double-blind fashion on 2 days at least 1 week apart. Indwelling intravenous cannulae were inserted in each forearm for drug administration and blood sampling. The cannulae were kept patent with 0.5 ml heparinised saline (200 units ml^{-1}). The subjects then rested supine for 30 min before baseline haemodynamic measurements were made. They remained recumbent throughout the infusion.

Nifedipine or vehicle alone were drawn up in black polyethylene syringes and administered through light protected lines because of the

photosensitivity of nifedipine. Each subject received a bolus of 0.15 ml kg^{-1} ($= 15 \mu\text{g kg}^{-1}$ nifedipine) intravenously over 5 min, flushed in with 50 ml of normal saline, followed by an infusion of 0.15 ml min^{-1} ($= 15 \mu\text{g min}^{-1}$ nifedipine) for 4 h.

Blood was taken for drug levels at 0, 5, 10, 15, 30 and 60 min and then hourly while on the infusion and for 4 h after infusion to determine the elimination half-life of nifedipine. The samples were immediately wrapped in aluminium foil to prevent photodegradation, and the plasma was separated by centrifugation under sodium light. The plasma was then frozen at -20°C , and protected from light until analysis.

As an additional control, six of the subjects received saline infusions given as above, on a third day. Local effects of the active preparations at the site of injection prevented these controls from being done in a double-blind fashion. Haemodynamic measurements were made but apparent hepatic blood flow was not measured nor were blood samples taken.

Study B Nifedipine solution was administered as in Study A but with 8 h infusions. The dose regimens are detailed in Table 1. Blood samples were taken during the infusion as in Study A and at 1, 2 and 4 h afterwards.

Haemodynamic measurements

Study A Blood pressure (BP) and heart rate (HR) were recorded semi-automatically (Dinamap II, Critikon) before drug administration and at 0, 5, 10, 15, 30 and 60 min and hourly thereafter during the infusion. Forearm blood flow (FBF) was measured by venous occlusion plethysmography, using mercury in silastic strain gauges and a filling pressure of 50 mm Hg. A wrist cuff obliterated the flow to the hand for 1 min before and during the readings (Whitney, 1953). Room temperature was kept constant at 23°C . Each flow value was the mean of five readings recorded over 1 min and analysed by hand (Greenfield *et al.*, 1963). FBF was recorded before and during infusion, at the times above.

Table 1 Study B: Dosage regimens

Group	Number	Bolus ($\mu\text{g kg}^{-1}$)	Infusion ($\mu\text{g min}^{-1}$)	Total dose (mg)
I	3	20	15	8.5
II	3	25	20	11.25
III	3	25	25 $\times$ 4 h and then 30 $\times$ 4 h	14.8

Apparent hepatic blood flow (AHBF) was measured as indocyanine green (ICG) clearance, following the rapid intravenous injection of 0.5 mg kg^{-1} body weight (Caesar *et al.*, 1961). Venous blood samples were taken at 2 min intervals from 6 to 14 min afterwards (Bax *et al.*, 1980). The plasma was separated by centrifugation and the optical density of the neat plasma measured at 805 nm by spectrophotometer. Calibration curves were prepared for each subject from his own blank plasma to which known concentrations of ICG were added. The curve was used to calculate ICG levels in plasma and hence clearance. Whole blood clearance was calculated as:

$$(\text{plasma clearance}) \times 100/1\text{-haemocrit}$$

AHBF was measured before nifedipine administration and again immediately before the end of the infusion.

Study B Haemodynamic measurements were made at the same time as in Study A but continued during the infusion and for 4 h afterwards.

Nifedipine assay

Nifedipine concentrations were assayed by gas liquid chromatography (courtesy of Miles Laboratories, Bridgend). This assay separates nifedipine from its pyridine metabolite and measures plasma nifedipine concentrations in

the range $5\text{--}140 \text{ ng ml}^{-1}$, with a coefficient of variation of 5.2% (A. Grant, personal communication).

Statistics

Differences between groups in pharmacokinetics and pharmacodynamics were analysed by analysis of variance. Differences between treatment days were analysed by Student's *t*-test for paired data. Results are expressed as mean $\pm$ s.e. mean.

Results

Pharmacokinetics

Study A Plasma concentrations reached a peak of $36 \pm 4.6 \text{ ng ml}^{-1}$ immediately after the bolus injection. The concentration fell rapidly and the mean half-life for this distribution phase was $0.25 \pm 0.01 \text{ h}$. A steady state concentration of $14.4 \pm 0.85 \text{ ng ml}^{-1}$ was attained within 2 h and maintained until the end of the infusion (Figure 1a). The terminal elimination half-life was $1.52 \pm 0.08 \text{ h}$. There was no significant variation in half-life, volume of distribution at steady state, or clearance of nifedipine between subjects (Table 2). Concentrations of the pyridine metabolite were in the range $0.1\text{--}0.5 \text{ ng ml}^{-1}$ during the infusion.

Figure 1 (a) Plasma nifedipine concentrations during Study A (4 h infusions). (b) Plasma nifedipine concentrations during Study B (8 h infusions), at three different doses. (Error bars omitted for clarity) Group I ●.....●, Group II ■---■, Group III ▲——▲.

Table 2 Study A: Pharmacokinetic data

Subject	$t_{1/2}$ (h)	K_d (h^{-1})	CL ($ml\ min^{-1}$)	V_{ss} ($l\ kg^{-1}$)	C_{ss} ($ng\ ml^{-1}$)
1	1.20	0.58	1250	1.80	12.0
2	1.64	0.42	1154	2.34	13.0
3	1.44	0.48	1282	2.16	11.7
4	1.41	0.49	1000	1.49	15.0
5	1.32	0.52	1034	2.01	14.5
6	1.72	0.40	1111	2.05	13.5
7	1.93	0.36	794	2.00	18.9
8	1.50	0.46	909	1.46	16.5
Mean	1.52	0.46	1067	1.91	14.4
$\pm$ s.e. mean	± 0.08	± 0.02	± 59	± 0.11	± 0.85

$t_{1/2}$ = elimination half-life; K_d = elimination coefficient; CL = (plasma) clearance (CL = dose $\times$ min $^{-1}$ $\times$ C_{ss}^{-1}); V_{ss} = (plasma) volume of distribution at steady state (V_{ss} = CL $\times$ K_d^{-1}); C_{ss} = (plasma) concentration at steady state.

Study B Plasma concentrations followed a time course similar to those in study A and steady state concentrations were reached within 2 h. Each group showed a rise in plasma concentration with increasing dose (Figure 1b). The pharmacokinetic data showed no differences between groups except in steady state concentration (Table 3).

Haemodynamics

Study A Pretreatment haemodynamic measurements were similar within subjects on all days. Nifedipine increased HR after the bolus (Table 4). This rise persisted for 45 min but was not sustained during the remainder of the infusion (Figure 2a). There was no change in HR with the vehicle alone.

Nifedipine and vehicle alone both reduced systolic BP (Table 4) and again, the effect was not sustained during the remainder of the infusion (Figure 2b).

FBF rose after the nifedipine bolus and to a lesser extent after the vehicle. This rise was not significantly sustained after either treatment (Figure 2c).

Saline infusion caused no significant haemodynamic change.

AHBF did not change significantly during nifedipine or vehicle infusion (Table 4).

Study B There were similar early changes in HR and FBF after the nifedipine bolus with all doses compared to control (Figure 3). Larger doses did not cause significantly greater effect. BP fell after the bolus, significant in groups II and III. Again, there were no sustained haemodynamic effects even at the highest doses (data not shown). Haemodynamic measurements during steady infusion did not change after the infusion was stopped.

ECG monitoring throughout showed no rhythm disturbances in either study.

Side effects

Study A Five subjects complained of mild headache and poor concentration while receiving nifedipine compared to none on vehicle-alone ($P = 0.012$ Fisher's Exact Probability Test). This headache generally developed 2–3 h after the start of the infusion. Four subjects (two each of nifedipine and vehicle) developed minor thrombophlebitis. Seven (four nifedipine, three vehicle) complained of a burning sensation at the site of bolus injection.

Table 3 Study B: Pharmacokinetic data (mean $\pm$ s.e. mean)

Group	$t_{1/2}$ (h)	K_d (h^{-1})	V_{ss} ($l\ kg^{-1}$)	CL ($ml\ min^{-1}$)	C_{ss} ($ng\ ml^{-1}$)
I	1.36 ± 0.25	0.59 ± 0.09	1.57 ± 0.05	884 ± 54	17.0 ± 1.42
II	2.00 ± 0.57	0.40 ± 0.09	3.31 ± 1.09	1129 ± 111	18.1 ± 1.96
III	2.01 ± 0.13	0.35 ± 0.03	2.50 ± 0.33	849 ± 59	35.7 ± 2.66
Mean	1.79 ± 0.21	0.42 ± 0.05	2.50 ± 0.41	954 ± 59	

No significant differences from Study A (except C_{ss}).
Abbreviations as for Table 2.

Table 4 Study A: Haemodynamic data (mean $\pm$ s.e. mean)

Variable	Treatment	Pretreatment	After bolus	3 h on infusion
Pulse (beats min ⁻¹)	Nifedipine	67.9 $\pm$ 3.3	82.8 $\pm$ 2.5***†	66.6 $\pm$ 3.1
	Vehicle	66.4 $\pm$ 3.7	67.0 $\pm$ 2.7	62.5 $\pm$ 3.6
	Saline	70.0 $\pm$ 3.9	69.2 $\pm$ 3.3	67.1 $\pm$ 4.8
Systolic BP (mm Hg)	Nifedipine	118.0 $\pm$ 4.8	108.9 $\pm$ 4.5†	114.6 $\pm$ 4.6
	Vehicle	117.1 $\pm$ 4.0	110.3 $\pm$ 3.3†	117.5 $\pm$ 4.4
	Saline	111.8 $\pm$ 5.4	111.7 $\pm$ 5.1	113.7 $\pm$ 6.1
Diastolic BP (mm Hg)	Nifedipine	66.1 $\pm$ 2.2	62.5 $\pm$ 3.0	68.1 $\pm$ 3.9
	Vehicle	67.0 $\pm$ 1.4	64.9 $\pm$ 2.4	67.4 $\pm$ 4.1
	Saline	56.5 $\pm$ 2.7	61.0 $\pm$ 3.4	60.5 $\pm$ 3.2
Forearm blood flow (% change) (ml min ⁻¹ 100 ml ⁻¹)	Nifedipine	(1.66 $\pm$ 0.15)	65.8 $\pm$ 21*†	21.3 $\pm$ 4.6
	Vehicle	(1.82 $\pm$ 0.29)	17.0 $\pm$ 7†	13.3 $\pm$ 14.7
	Saline	(1.95 $\pm$ 0.13)	5.0 $\pm$ 9	-7 $\pm$ 9.6
Apparent hepatic blood flow (ml min ⁻¹ kg ⁻¹)	Nifedipine	30.1 $\pm$ 5.1	—	25.8 $\pm$ 4.2
	Vehicle	26.3 $\pm$ 3.8	—	22.0 $\pm$ 3.3

* $P < 0.05$ and ** $P < 0.01$ compared to value on vehicle.

† $P < 0.05$ and †† $P < 0.01$ compared to pretreatment value.

Study B Eight subjects had a burning sensation during bolus injection. Five had headache and drowsiness during the infusion. Two had objective facial flushing after the bolus. One in group III developed thrombophlebitis at the site of the infusion within 24 h of the study.

Discussion

Nifedipine has been investigated as an agent to reduce myocardial infarct size. Early intervention trials using oral nifedipine have not shown any benefit and have tended to show increased infarct size or mortality (Muller *et al.*, 1984; Sirnes *et al.*, 1984; Wilcox *et al.*, 1986). The tachycardia caused by an oral or intravenous bolus dose of nifedipine might harm patients with acute infarction, by raising myocardial oxygen demand. An intravenous infusion on the other hand could maintain a steady nifedipine concentration and avoid harmful haemodynamic effects.

Our studies show that infusion of nifedipine can rapidly achieve and maintain steady state plasma concentrations in the range seen in normal clinical usage of oral nifedipine (Stern *et al.*, 1984; Beerahee *et al.*, 1985). Acute haemodynamic changes occurring after bolus injection are not sustained during prolonged infusion. In addition, these results suggest that the vehicle alone may have important haemodynamic effects.

Nifedipine has been widely used clinically despite little pharmacokinetic data. There has

only been one small study of nifedipine given by intravenous infusion (Raemisch & Ziegler, 1985) and no infusion dose-ranging study before. Our pharmacokinetic data are similar to those reported after intravenous bolus or short intravenous infusion (Kleinbloesem *et al.*, 1984b; Foster *et al.*, 1983). Raemisch & Ziegler (1985) found that infusions of 24 h duration seemed to prolong elimination half-life. They suggested that the fall in plasma nifedipine concentration after bolus injection represents a prolonged distribution phase rather than a true elimination phase which is not usually seen because nifedipine concentrations fall below the limit of detection. We did not find a prolonged elimination half-life but the duration of our infusion may have been too short. The elimination half-life seen in our studies is shorter than that reported after oral administration, and so infusion may allow finer control over plasma nifedipine concentrations.

Up to 17% of the population may be slow metabolisers of nifedipine (Kleinbloesem *et al.*, 1984d), although this is disputed (Beerahee *et al.*, 1985). We found less intersubject variation after intravenous administration than is reported after other modes of administration. Although our sample is small, the results suggest that the variation seen after oral administration is due mainly to variable first pass metabolism (Waller *et al.*, 1984).

Our results confirm the previously reported acute haemodynamic effects of nifedipine (Kleinbloesem *et al.*, 1984b,c; Raemisch &

Figure 2 Haemodynamic changes in Study A, during infusion of nifedipine ●—● Vehicle alone ▲---▲, and saline ■····■ (Error bars omitted for clarity). * $P \leq 0.05$ compared with baseline.

Sommer, 1983; Foster *et al.*, 1983), but suggest that some of the effects at least with this preparation may be due to the vehicle. Immediately after the bolus of nifedipine, arterial vasodilation reduces BP, and increases HR by reflex sympathetic stimulation. Surprisingly, the vehicle alone causes a similar fall in BP, although with less vasodilation and no rise in HR. Clearly, the vehicle is pharmacodynamically active. A similar vehicle is used for many of the dihydropyridine calcium antagonists, but even supposedly controlled studies of these drugs have used only saline placebos (Iliopoulou *et al.*, 1983).

The haemodynamic effects after the bolus did not persist during the continuous infusion. One possible exception is the vasodilation, evidenced not by the FBF but by the headache which came on after 1–2 h and lasted for several hours afterwards. The lack of detectable haemodynamic changes during infusion might be due to inadequate plasma concentrations but steady state plasma concentrations in study B without haemodynamic effect were similar to those after bolus injection with marked haemodynamic effects in all groups. The rate of change of nifedipine concentration may be responsible for the

Figure 3 Maximum haemodynamic changes in each group in Study B, during the first 15 minutes after nifedipine bolus injection (mean $\pm$ s.e. mean). ** $P \leq 0.01$ compared with baseline.

acute haemodynamic effects, and slow gradual infusion may avoid the initial rise in pulse rate or acute hypotension. Gradual administration by slow-release tablet, by a rectal osmotic preparation and by slow i.v. infusion without bolus blunts the early tachycardia although the hypotensive effect still occurs (Kleinbloesem *et al.*, 1984c, 1985). Our data suggest that cardiovascular adaptation is rapid. This may be due to baroreceptor resetting (Kiowski *et al.*, 1983), or to local autoregulation.

Neither nifedipine nor vehicle significantly affected AHBf. Feely (1984) has shown that 10 mg nifedipine sublingually increased AHBf measured by ICG, in proportion to a fall in blood pressure. Since hypotension alone lowered AHBf, Feely *et al.* (1982) suggested that nifedipine has a direct vasodilating effect, as demonstrated in animal isolated portal vein (Vanhoutte, 1981). In dogs, nifedipine reduced hepatic blood flow (measured by direct hepatic vein cannulation) proportional to the fall in aortic pressure, in a dose related fashion (Hamann *et al.*, 1984). Further, at high doses, nifedipine underwent reduced clearance as a result. The doses used in that study were equivalent to 12.3–83 $\mu\text{g min}^{-1}$ in a 65 kg man, considerably larger than in our study. The differences are therefore probably dose related. Kleinbloesem *et al.* (1984f), in a study of six volunteers, found that prolonged nifedipine infusion of 1.3 mg h^{-1} (compared to 0.9 mg h^{-1} in our study) caused a 20% rise in AHBf and a fall in diastolic blood pressure of 9 mm Hg. The lack of effect on AHBf in our study may be explained by the lack of haemo-

dynamic changes at the time of the second ICG clearance measurement. Single oral dosing with nisoldipine and verapamil causes an increased ICG clearance even in the absence of haemodynamic changes, which returns to normal with chronic oral dosing (Meredith *et al.*, 1985a,b). Our data indicate that, like other haemodynamic parameters, AHBf is not changed by prolonged i.v. administration of nifedipine. Thus, nifedipine pharmacokinetics are unlikely to be altered by liver blood flow at the doses used here.

Two categories of side effects were seen: headache and flushing, due to vasodilation, and thrombophlebitis and pain on bolus injection, most probably due to the irritant vehicle. This latter finding suggests that only low doses of this preparation of nifedipine ($< 25 \mu\text{g min}^{-1}$) should be infused through a peripheral line for any prolonged period. Higher doses will need central line infusion or dilution.

In conclusion, this study is the only double-blind comparison of i.v. infusion of nifedipine and its vehicle in human subjects. The results are in keeping with previous work with nifedipine but indicate that the vehicle in the parenteral preparation of nifedipine and other calcium antagonists may have independent haemodynamic properties. We urge caution when interpreting studies of the intravenous use of dihydropyridine calcium antagonists and emphasise the need for proper controls.

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